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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/903,993	NILSSON ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *11 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12-22 and 24-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 July 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a response to the "Election under 35 U.S.C. §121" filed 13 November 2002 (Paper No. 8). Claims 1-28 are pending in the application.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-10, 12-22 and 24-28) and the species of Diabetes Type II in Paper No. 8 is acknowledged. The Election indicates that claims 43-61 are included in Group I; however, as the case does not contain claims numbered beyond 28 and the original election filed June 7, 2002, which is cited in Paper No. 8, does not refer to claims 43-61, it is assumed that reference to claims 43-61 is a typographical error.

Claims 11 and 23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-10, 12-22 and 24-28 are presently under consideration.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

The citizenship of Lars Nilsson has been altered without initial and date.

Drawings

The drawings are objected to for the reasons indicated on the attached PTO-948. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.

Specification

The disclosure is objected to because of the following informalities: The specification contains misspelled words such as "corrsing" on page 17, line 22. Applicant is urged to carefully review the specification and correct any typographical errors therein.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 and 24-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The instant claims 1-17 and 25-27 are directed to a transgenic mouse whose genome comprises a normal, mutant or altered transgene encoding a protease inhibitor operably linked to a promoter effective for expression of said gene in the brain tissue of said mouse and methods of

using said transgenic mouse. In dependent claims, the mouse is further limited to comprising a second transgene comprising a DNA sequence encoding a normal, mutant or altered gene encoding tau-i, apolipoprotein E, APP, presenilin 1, presenilin 2, IL-1 alpha, or IL-1 beta and the transgene is limited to a normal, mutant or altered gene encoding antichymotrypsin, anti-trypsin, alpha-2-macroglobulin, BACE or a Kunitz inhibitor-containing protein. Claims 24 and 28 are directed to a method of using any transgenic mouse model of Alzheimer's disease. Thus, the claims encompass, or require as an essential component of the method, a broad genus of any and all mice comprising a normal, mutant or altered transgene encoding any and all protease inhibitors presently known or to be discovered. On page 14, the specification discusses the properties of a mutant or altered protein in general terms, suggesting that some functional activity is desired and describes methods for modifying protease inhibitor protein genes. The mutant or altered genes of the claims are not, however, limited to encoding proteins having any function; thus, the more narrow embodiments encompass normal, mutant or altered transgene encoding antichymotrypsin, anti-trypsin, alpha-2-macroglobulin, BACE or a Kunitz inhibitor-containing protein wherein the encoded polypeptides are non-functional or function in some way other than the native protein.

The Guidelines for Written Description state "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus", "In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Federal Register, Vol. 66, No. 4, Column 2, page 71436). For reasons that are set forth in detail herein below regarding enablement for the claims, the phenotype arising from expression of any given

transgene in a transgenic animal is highly unpredictable. Thus, to demonstrate possession of the full genus of transgenic animals encompassed by the claims it is incumbent upon Applicant to describe a sufficient number of species of said genus, both genotypically and phenotypically, such that the species described adequately reflect the variation within the genus.

The instant disclosure provides examples of transgenic mice comprising a single normal transgene encoding a protease inhibitor (i.e. the normal human alpha-1-antichymotrypsin gene) under the control of a GFAP promoter, wherein said transgenic mice do not comprise any additional transgenes or further comprise an hAPP(V717F) transgene or homozygous disruption of an endogenous ApoE gene. However, these examples are far from representative of the very broad genus encompassed by the claims, which includes mice expressing transgenes having functional properties that are dramatically different from the transgenes reduced to practice in the application.

In the absence of representative species, the written description requirement for a claimed genus may be satisfied by disclosure of the relevant characteristics that identify the genus (see MPEP 2163 (ii)). In the instant case, the claims encompass such enormous breadth that it would not be possible to identify non-trivial characteristics that are even common to the entire genus, let alone features that are sufficiently characteristic that they would serve to identify the members of the genus over its full scope. For example, the phenotype of a transgenic mouse comprising a transgene encoding an inhibitor of a protease that is not expressed in neuronal cells will likely have little or nothing in common with the mice reduced to practice in the claims beyond those features that are common to a wild-type mouse. Furthermore, there is nothing in the disclosure that would allow the skilled artisan to envision the phenotypic characteristics of

even narrow embodiments such as the claimed anti-trypsin transgenic mouse, as there is nothing to suggest that the anti-trypsin transgenic mouse would be phenotypically the same as the alpha-1-antichymotrypsin transgenic mouse or to indicate how the anti-trypsin transgenic mouse would differ from the alpha-1-antichymotrypsin mouse.

The claims additionally encompass transgenic mice, and methods of using said mice, comprising a transgene under the control of any and all promoters effective for expression of a transgene in the brain. However, the disclosure provides only a single example of a promoter having the claimed characteristics and merely states, "is [sic] should be noted that other promoters that are capable of directing protein expression in the brain and optionally in other tissues from an operably attached transgene are suitable for use in the present invention" (page 16, paragraph 1). The Guidelines for Written Description state, "The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art" (Federal Register, Vol. 66, No. 4, Column 3, page 71434). In the instant case, the promoter effective for expression of a transgene in the brain is clearly a critical element, as the claims are specifically limited to a transgene comprising the promoter. The description provided in the specification does not, however, support any such promoter beyond the GFAP promoter reduced to practice. An adequate written description of a DNA requires more than a mere statement that it is part of the invention; what is required is a description of the DNA itself. It is not sufficient to define DNA solely by its principal biological property, i.e. it directs protein expression in the brain, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Also, naming a type of material

generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all DNA's that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). With respect to the method claims, adequate description of the methods first requires an adequate description of the materials, i.e. specific DNA sequences, which provide the means for practicing the invention.

Claim 28 is further rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description for the various genera of compounds having the activity of an inhibitor of an interaction between A-beta peptide and antichymotrypsin, an inhibitor of an interaction between A-beta peptide and apolipoprotein E, an inhibitor of antichymotrypsin expression, an inhibitor of apolipoprotein E expression, an inhibitor of APP expression, or an inhibitor of expression of an A-beta peptide. Again the compounds are critical elements in the claimed method as the claim is specifically limited to compounds having the recited activity. The disclosure, however, provides neither specific examples that would be representative of the entire genus of molecules having the recited function nor a description of the relevant identifying characteristics that would distinguish the compounds having the recited function.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of transgenic animals or methods claimed. Therefore, only the described

transgenic animals, and methods of using said transgenic animals, comprising the wild-type human alpha-1-antichymotrypsin transgene under the transcriptional control of the GFAP promoter or comprising the wild-type human alpha-1-antichymotrypsin transgene under the transcriptional control of the GFAP promoter and the PDGF-hAPP(V717F) with or without a functional endogenous ApoE gene, or the method of claim 24 wherein the activity of said compound is not limited or limited to an anti-inflammatory agent meet the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-17 and 24-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse, or methods of using said transgenic mouse, whose genome comprises a transgene comprising a DNA sequence encoding a normal alpha-1-antichymotrypsin operably linked to a GFAP promoter, wherein the mouse might further comprise a second transgene encoding the hAPP(V717F) protein and/or a homozygous knockout of the endogenous ApoE gene and wherein said mice have a phenotype of exacerbated β-amyloidosis, cognitive impairment as measured by radial arm water maze, and hyperphosphorylation of tau, does not reasonably provide enablement for mice comprising transgenes encoding protease inhibitors other than alpha-1-antitrypsin, additional transgenes other than hAPP(V717F) or knockouts other than ApoE, or for transgenic mice wherein expression of the ACT gene produces symptoms other than those reduced to practice in the application. The specification does not enable any person skilled in the art to which it pertains,

or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention: The instant invention is directed to mice comprising a transgene encoding a protease inhibitor expressed in the brain, and methods of using transgenic mice to screen for compounds potentially useful in the treatment of Alzheimer's disease.

Breadth of the claims: As described herein above, the claims broadly encompass a genus of mice comprising a normal, mutant or altered transgene encoding any and all protease inhibitors or, in more narrow embodiments, normal, mutant or altered transgene encoding antichymotrypsin, anti-trypsin, alpha-2-macroglobulin, BACE or a Kunitz inhibitor-containing protein wherein the encoded polypeptides are non-functional or function in some way other than the native protein. The claims are further directed to mice comprising the protease inhibitor transgene and further comprising normal, mutant or altered genes encoding a variety of Alzheimer's disease associated proteins as well as cell lines established from the mice and methods of using the mice. Further, the claims are directed to the transgenic mice having the

genotypes set forth herein above and a variety of phenotypes broadly classified as amyloidogenic diseases. The enabling disclosure must teach the skilled artisan how to make and use the claimed invention commensurate with the full scope of the claimed subject matter. Thus the teachings of the specification and prior art must enable one of ordinary skill in the art to make all of the transgenic animals having the claimed phenotypes, how to use transgenic animals comprising all of the transgenes set forth in the claims either alone or in combination, and how to practice the methods using all of the animals encompassed by the method claims.

State of the prior art and level of predictability in the art: First, the art generally teaches that the phenotype arising from insertion or deletion of even a well-characterized gene in a transgenic animal is highly unpredictable. Doetchman (1999) *Lab. Animal Sci.* 49:137-143 teaches, "[o]ne often hears the comment that genetically engineered mice...are not useful because they frequently do not yield the expected phenotype, or they don't seem to have any phenotype. These expectations are often based on years of work, and in some instances, thousands of publications of mostly in vitro studies" (page 137, paragraph 1). Doetchman goes on to teach, "it has become clear that genetic background plays an important role in the susceptibility of mice to many disorders. Therefore, the phenotypes of knockout mouse strains will also have genetic background dependencies" (page 140, column 2, third full paragraph) and "[a]pparent lack of phenotype more likely reflects our inability to ask the right questions, or our lack of tools to answer them" page 142, first paragraph. These teachings point out that the phenotype arising from any given mutation or genetic manipulation of a transgenic mouse is highly unpredictable and in many cases cannot be revealed by routine experimentation. Thus the skilled artisan would not predict success in producing animals having symptoms similar to any

amyloidogenic diseases other than Alzheimer's disease using the teachings of the instant disclosure and prior art.

Regarding the production of mice having symptoms similar to human Alzheimer's disease other than those reduced to practice in the disclosure, Snow *et al.* (1997) WO 97/46664 teaches, "[p]revious animal models overexpressing a specific amyloid protein only rarely produce some of the pathology associated with different amyloid diseases, or produce fibrillar amyloid in a different location than that observed clinically in humans, making it extremely difficult to screen *in vivo* for potential therapeutics for amyloid diseases" (page 12, second full paragraph). Thus Snow *et al.* teaches that the general unpredictability of phenotype arising from genotypic manipulation of animals taught by Doetchman extends to amyloid proteins and amyloid diseases. Furthermore, Nilsson *et al.* (2001) *J. Neurosci.* 21:1444-1451 casts doubt on the likelihood of an Alzheimer's-like phenotype arising from the expression of protease inhibitors other than ACT, as Nilsson *et al.* teaches that the interaction of ACT with Aβ peptide likely plays a part in its association with Alzheimer's disease amyloid core filaments (see especially the first paragraph on page 1444) and that even closely related protease inhibitors lack the Aβ peptide interaction domain and thus would not produce an Alzheimer's-like phenotype (see especially the second full paragraph in the second column on page 1444). Therefore, the skilled artisan would not expect that an Alzheimer's-like phenotype would be a general feature of the genus of mice claimed in the application.

Amount of direction provided by the inventor and existence of working examples: The instant disclosure provides general teachings regarding how to make transgenic mice and how to use mice having an Alzheimer's-like phenotype to screen for drugs that might be useful in the

treatment of Alzheimer's disease. The disclosure reduces to practice transgenic mice comprising a normal human alpha-1-antichymotrypsin transgene and mice comprising the human alpha-1-antichymotrypsin transgene which further comprise hAPP(V717F) transgene in the presence and absence of homozygous disruption of the endogenous ApoE gene, and establishes a phenotype associated with those genotypic modifications consisting of exacerbated β-amyloidosis, cognitive impairment as measured by radial arm water maze, and hyperphosphorylation of tau. However, the specification fails to address the unpredictability of the phenotype arising from the many genotypes encompassed by the claims for which no phenotype has been established. In fact, teachings in the specification indicate that it is very likely that few, if any, of the claimed mice would have an Alzheimer's-like phenotype. Applicant teaches, "[s]ince the demonstration that ACT and apoE...are amyloid promoter *in vitro*, many other proteins have been tested for their possible effect on Aβ polymerization...ACT and apoE are the only such molecules for which genetic studies support their involvement in the Alzheimer pathogenic pathway" (second paragraph on page 5).

With regard to making mice having amyloidogenic disease-like phenotypes other than Alzheimer's disease, the specification is silent with regard to how this might be accomplished using any protease inhibitor gene alone or in combination with other genetic manipulations. The specification does not teach any phenotypic characteristics in the mice reduced to practice that would be associated with amyloidogenic diseases other than Alzheimer's disease, and does not suggest that other protease inhibitors might be associated with other types of amyloidogenic diseases. Given these teachings the skilled artisan would not predict that any of the claimed genotypes would give rise to any phenotype other than an Alzheimer's disease-like phenotype.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, given the art-recognized unpredictability of the phenotype arising from disruption of any given gene in a mouse, the skilled artisan would have to resort to trial and error experimentation in order to uncover a useful phenotype associated with each of the different genotypes encompassed by the claims. Likewise, the teachings of the specification and prior art do not enable the skilled artisan to establish animal models of any amyloidogenic disease other than Alzheimer's disease. Given the breadth of the claims and the absence of any guidance in the disclosure or prior art that would enable the skilled artisan to make or use embodiments of the claimed invention other than those reduced to practice, practicing the invention commensurate with the full scope of the claimed subject matter would clearly require undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7, 24 and 25-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 is indefinite in its recitation of a limitation as a derivative of some starting material (i.e. cell line derived from the mouse). Without a clear statement of the process by which the starting material is derivatized it is not possible to know the metes and bounds of such a limitation because any given starting material can have many divergent derivatives depending

on the process of derivatization. Amending the claim such that it is directed to a cell line established from or obtained from the mouse would obviate this rejection.

Claim 24, and claims 25-28 as they depend therefrom, are indefinite in the recitation of "transgenic mice" in line 4 of claim 24. There is insufficient antecedent basis for the limitation in the preamble, which recites "transgenic animal" in line 1. Amending the preamble to match the body of the claim would be remedial.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, 6 and 8 are rejected under 35 U.S.C. 102(a) as being anticipated by Mucke *et al.* (1999) *Soc. Neurosci. Abstr.* 25:302.

Mucke *et al.* teaches a transgenic mouse comprising a transgene encoding a normal protease operably linked to a promoter effective for expression of said transgene in the brain tissue of said mouse according to claim 1. The transgenic mouse of Mucke *et al.* further comprises an APP transgene according to claim 2, a GFAP promoter according to claim 3, a human antichymotrypsin transgene according to claims 5 and 6, and a phenotype associated with expression of the antichymotrypsin transgene that is essentially similar to human Alzheimer's disease according to claim 8. The transgenic mouse taught by Mucke *et al.* is the same as the mouse taught in the instant application; therefore, the limitations of the claims are taught by Mucke *et al.*

Claims 1, 5, 6 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by either one of Yeung *et al.* (1994) *J. Cell. Biochem. Suppl.* 0:164 or Kuljis *et al.* (1993) *Soc. Neurosci. Abstr.* 19 :1035.

Yeung *et al.* and Kuljis *et al.* each teach a transgenic mouse comprising a transgene encoding a normal protease operably linked to a promoter effective for expression of said transgene in the brain tissue of said mouse according to claim 1. The transgenic mouse of either of Yeung *et al.* and Kuljis *et al.* comprise a human antichymotrypsin transgene according to claims 5 and 6, and a phenotype associated with expression of the expression of the antichymotrypsin transgene that is essentially similar to human Alzheimer's disease according to claim 8. The transgenic mouse taught by Yeung *et al.* and Kuljis *et al.* is the same as the mouse taught in the instant application; therefore, the limitations of the claims are taught by Yeung *et al.* and Kuljis *et al.*

Claims 20 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Kobayashi *et al.* (1994) *Neurosci. Lett.* 172:147-150.

Kobayashi *et al.* teaches a method comprising providing a mammalian cell, administering to said cell antichymotrypsin and a compound (i.e. β_{25-40}) and monitoring cell death or neurite outgrowth (i.e. low density cultures) according to the limitations of claims 20 and 21 (see especially Figure 3 and the caption thereto). The method taught by Kobayashi *et al.* is the same as the method set forth in the claims; therefore, the claims are anticipated by Kobayashi *et al.*

Claims 24-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Snow *et al.* (1997) WO 97/46664 as evidenced by Anger *et al.* (1991) *Neurotoxicol.* 12:403-413.

Snow *et al.* teaches a method of screening compounds for treatment of Alzheimer's Disease comprising providing a transgenic animal model of Alzheimer's disease, administering a compound and measuring the effect on behavior in said mouse "utilizing standard memory tests known to those skilled in the art" (see especially the paragraph bridging pages 85 and 86). Anger *et al.* teaches that the radial arm water maze is a standard memory test known to those skilled in the art (see especially the first full paragraph on page 408 and references cited therein, and the paragraph bridging pages 408 and 409). Snow *et al.* further teaches that changes in behavioral tests in treated animals relative to untreated animals is indicative of a compound useful for treating Alzheimer's disease. Thus, Snow *et al.* teaches all of the limitations of claim 24. Snow *et al.* goes on to teach that alpha-1-antichymotrypsin is an important component of Alzheimer's disease amyloid (first full paragraph on page 34) and that alpha-1-antichymotrypsin, among other proteins, "may be utilized for the production of new transgenic animals and/or transfected cells" (page 35, lines 6-8). Thus, Snow *et al.* teaches the method according to claim 24 wherein the transgenic mouse comprises antichymotrypsin according to claims 25 and 26. The method taught by Snow *et al.* is the same as the method taught in the instant application; therefore, the limitations of the claims are met by Snow *et al.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 7, 10, 12, 13 and 15-17 rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Mucke *et al.* (supra), Yeung *et al.* (*supra*) or Kuljis *et al.* (*supra*) in view of Snow *et al.* (*supra).*

The teachings of Mucke *et al.*, Yeung *et al.* and Kuljis *et al.* pertaining to the transgenic animal of claim 1, and claims 7, 10, 12, 13 and 15-17 insofar as they depend from claim 1, are

set forth herein above. Mucke *et al.*, Yeung *et al.* and Kuljis *et al.* do not teach a primary cell culture derived from the animal according to claim 7, or methods of screening compounds comprising monitoring a pathological or cognitive marker of Alzheimer's disease (claim 10), monitoring the phosphorylation state of tau protein (claims 12 and 13), monitoring the formation or aggregation of protein filaments (claim 15), or monitoring neuronal cell death or synapse loss by neurofilament antibody staining (claims 16 and 17) using the transgenic mouse of claim 1.

Snow *et al.* teaches a transgenic animal model of Alzheimer's disease and that the animal is primarily useful for screening agents for potential therapeutic effect. In Examples 8-10 (beginning on page 76), Snow *et al.* teaches establishment of a transgenic animal model of Alzheimer's disease, and in the paragraph bridging pages 85 and 86 teaches, " transgenic animals...or animal cells derived from transgenic animals, can be used to screen compounds for a potential effect on the treatment of Alzheimer's disease". In Example 11, Snow *et al.* provides detailed instruction regarding various markers that can be used to assess a compound's effectiveness. In the paragraph bridging pages 85 and 86, Snow *et al.* generally teaches that pathological or cognitive markers of Alzheimer's disease can be monitored in the mice according to the instant claim 10. In the paragraph bridging pages 89 and 90, Snow *et al.* identifies hyperphosphorylation of tau as a marker of Alzheimer's disease that can be monitored according to the instant claims 12 and 13. In the paragraph bridging pages 89 and 90, Snow *et al.* also teaches monitoring changes in cytoskeletal markers as indicators of Alzheimer related changes according to the instant claim 15. Finally, Snow *et al.* teaches monitoring cell death or synapse loss, which method comprises monitoring cytoskeletal markers according to claims 16 and 17 (see especially the paragraph bridging pages 92 and 93 and the first full paragraph on page 93).

The teachings described above demonstrate that, at the time the instant application was filed, both the transgenic mouse of the instant application and methods of using the mouse were known to one skilled in the relevant art. Further, it would have been obvious to one of ordinary skill in the art at the time the instant application was filed to combine these teachings according to the limitations of the claimed invention. Motivation to combine these teachings comes from Snow *et al.* First, Snow *et al.* generally teach, "only some of the Alzheimer's disease neuropathology is observed in current animal models of the diseases...Thus, there is a need for the development of new transgenic animal models of the amyloid diseases including Alzheimer's disease. In addition, there is a need for new cell culture models to rapidly screen and identify new lead therapeutics for each of the amyloid diseases" (paragraph bridging pages 7 and 8). This teaching points out a deficiency in the art that would lead one to pursue new animal models of Alzheimer's disease. Snow *et al.* then goes on to teach that alpha-1-antichymotrypsin is an important component of Alzheimer's disease amyloid (first full paragraph on page 34) and that alpha-1-antichymotrypsin, among other proteins, "may be utilized for the production of new transgenic animals and/or transfected cells" (page 35, lines 6-8). Therefore, based on the teachings of Snow *et al.*, the skilled artisan would be motivated to practice the methods of Snow *et al.* with a variety of animal models of Alzheimer's disease, and the alpha-1-antitrypsin transgenic mouse of Mucke *et al.*, Yeung *et al.* and Kuljis *et al.* in particular. Absent evidence to the contrary, the skilled artisan would predict success in practicing the methods of Snow *et al.* using the mouse of Mucke *et al.*, Yeung *et al.* or Kuljis *et al.* because the methods are generally applicable to any animal model of Alzheimer's disease.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
February 6, 2003

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER